EXHIBIT A
MARKED-UP VERSION OF SUBSTITUTE SPECIFICATION

TITLE OF THE INVENTION

Transdermal drug delivery system for oxybutynin.

INCORPORATION BY REFERENCE

This application claims priority benefits of German Patent Application No. DE 102 51 256.6 filed November 4, 2002.

FIELD OF THE INVENTION

The invention concerns a transdermal drug delivery system (TDS) comprising

- a cover which is impermeable for the active ingredient,
- a matrix containing oxybutynin as active ingredient and
- a facultative release liner, wherein the matrix further comprises
- an *Aloe Vera* extract,
- a pressure sensitive adhesive and
- a cross linking agent for the adhesive.

BACKGROUND

WO 99/48 493 describes an oxybutynin patch obtained according to the ~~so~~called so-called hot melt process. It is stated that the patch does not contain any enhancer. Nevertheless substances which are usually used as enhancers, are mentioned, especially citric acid triester.

U.S. Pat. No. 5,601,839 describes triacetin as an agent improving permeability.

As regards oxybutynin patches, U.S. Pat. No. 5,411,740 and WO 93/23 025 should also be mentioned.

Citation or identification of any document in this application is not an admission that such document is available as prior art to the present invention.

SUMMARY OF THE INVENTION

The problem underlaying the invention is solved by a transdermal drug delivery system (TDS) comprising

- a cover which is impermeable for the active ingredient,
- a matrix containing oxybutynin as active ingredient and
- a facultative release liner, wherein the matrix further comprises
- an ~~Aloe Vera~~*Aloe vera* extract,
- a pressure sensitive adhesive and
- a cross linking agent for the adhesive.

Accordingly, it is an object of the invention to not encompass within the invention any previously known product, process of making the product, or method of using the product such that Applicants reserve the right and hereby disclose a disclaimer of any previously known product, process, or method. It is further noted that the invention does not intend to encompass within the scope of the invention any product, process, or making of the product or method of using the product, which does not meet the written description and enablement requirements of the USPTO (35 U.S.C. 112, first paragraph) or the EPO (Article 83 of the EPC), such that Applicants reserve the right and hereby disclose a disclaimer of any previously described product, process of making the product, or method of using the product.

It is noted that in this disclosure and particularly in the claims and/or paragraphs, terms such as "comprises", "comprised", "comprising" and the like can have the meaning attributed to it in U.S. Patent law; e.g., they can mean "includes", "included", "including", and the like; and that terms such as "consisting essentially of" and "consists essentially of" have the meaning ascribed to them in U.S. Patent law, e.g., they allow for elements not explicitly recited, but exclude elements that are found in the prior art or that affect a basic or novel characteristic of the invention.

These and other embodiments are disclosed or are obvious from and encompassed by, the

following Detailed Description.

DETAILED DESCRIPTION

The transdermal drug delivery system (TDS) comprises

- a cover which is impermeable for the active ingredient,
- a matrix containing oxybutynin as active ingredient and
- a facultative release liner, wherein the matrix further comprises
    - an *Aloe vera* extract,
    - a facultative skin care agent,
    - a pressure sensitive adhesive and
    - a cross linking agent for the adhesive.

The transdermal drug delivery system according to the invention may comprise racemic oxybutynin, R-oxybutynin, S-oxybutynin or desethyl-oxybutynin.

Further, the pressure sensitive adhesive of the transdermal drug delivery system according the invention may comprise or consist of an acrylate based polymer, preferably a polymer based on an acrylate-vinyl acetate copolymer.

Further, the pressure sensitive adhesive of the transdermal drug delivery system according to the invention may comprise or consist of Durotak 2287 (polyacrylate adhesive) or Durotak 2516 (acrylate-vinyl acetate adhesive).

Further, the matrix of the transdermal drug delivery system according to the invention may comprise Ti-acetylacetonate, Al-acetylacetonate or polybutyl-titanate as crosslinking agent.

Further the extracting agent of the ~~Aloe Vera~~*Aloe vera*-extract of the transdermal drug delivery system according to the invention may be a vegetable oil, preferably soybean oil.

An ~~Aloe Vera~~*Aloe vera*-extract is available from, for example, Caesar & Loretz (Hilden/Germany).

Further, the ~~Aloe Vera~~*Aloe vera*-extract of the transdermal drug delivery system according to the invention may comprise 5 to 15% by weight of ~~Aloe Vera~~*Aloe vera* oil and 95 to 85% by weight of the vegetable oil.

Further, the matrix of the transdermal drug delivery system according to the invention may comprise the ~~Aloe Vera~~*Aloe vera*-extract as the only enhancer.

Further, the matrix of the transdermal drug delivery system according to the invention may comprise 5 to 40, preferably 10 to 35 and especially 15 to 30% by weight of oxybutynin (based on the matrix).

Further, the matrix of the transdermal drug delivery system according to the invention may comprise 10 to 25, preferably 12 to 20 and especially 14 to 18% by weight of ~~Aloe Vera~~*Aloe vera*-extract (based on the matrix).

Further, the matrix of the transdermal drug delivery system according to the invention may comprise 0.1 to 5.0, preferably 0.3 to 3 and especially 0.5 to 2.0% by weight of the crosslinking agent (based on the matrix).

The transdermal drug delivery system according to the invention may have a surface of 5 to 80, preferably 10 to 60 and especially 20 to 50 cm^2.

The invention will now be further described by way of the following non-limiting examples which further illustrate the invention, and are not intended, nor should they be interpreted to, limit the scope of the invention.

~~Example and comparative example~~EXAMPLES

A composition of a matrix according to the invention was provided as follows:

Oxybutynin	20.0%
~~Aloe Vera~~Aloe vera-extract (soy bean oil) 15.0%	
Ti-acetylacetonate (Tyzor AA 75)	1.3%
Durotak 2287 (polyacrylate adhesive)	remainder

This composition was subjected to a permeation test (mouse skin). The maximum flux was 9.2 $\mu g/cm^2/h$. The permeation was 190 $\mu g/cm^2/24$ h.

According to U.S. Pat. No. 5,601,839 a matrix was provided with the following composition

Oxybutynin	20.0%
Triacetin	15.0%
Al-Acetylacetonate	0.5%
Durotak2051 (Acrylate/Vinylacetate adhesive)	remainder

This composition was also subjected to a permeation test (mouse skin). The maximum flux was 5.3 $\mu g/cm^2/h$. The permeation was 80 $\mu g/cm^2/24$ h.

WHAT IS CLAIMED IS ~~Claims~~

1. Transdermal drug delivery system (TDS) comprising
- a cover which is impermeable for the active ingredient,
- a matrix containing oxybutynin as active ingredient and
- a facultative release liner, wherein the matrix further comprises
- an Aloe Vera extract,
- a pressure sensitive adhesive and
- a cross linking agent for the adhesive.

2. Transdermal drug delivery system according to claim 1, comprising racemic oxybutynin, R-oxybutynin, S-oxybutynin or desethyl-oxybutynin.

3. Transdermal drug delivery according to claim 1, wherein the pressure sensitive adhesive of the matrix is comprised of an actrylate based polymer, preferably a polymer based on an acrylate-vinyl acetate copolymer.

4. Transdermal drug delivery system according to claim 1, wherein the matrix is comprised of Durotak 2287 or Durotak 2516.

5. Transdermal drug delivery system according to claim 1, wherein the matrix comprises Ti-acetylacetonate, Al-acetylacetonate or polybutyl-titanate as crosslinking agent.

6. Transdermal drug delivery system according to claim 1, wherein the extracting agent of the Aloe Vera-extract is a vegetable oil, preferably soybean oil.

7. Transdermal drug delivery system according to claim 6, wherein the Aloe Vera-extract comprises 5 to 15% by weight of Aloe Vera oil and 95 to 85% by weight of vegetable oil.

8. Transdermal drug delivery system according to claim 1, wherein the matrix comprises the Aloe Vera-extract as the only enhancer.

9. Transdermal drug delivery system according to claim 1, wherein the matrix comprises 5 to 40, preferably 10 to 35 and especially 15 to 30% by weight of oxybutynin (based on the matrix).

10. Transdermal drug delivery system according to claim 1, wherein the matrix comprises 10 to 25, preferably 12 to 20 and especially 14 to 18% by weight of Aloe Vera-extract (based on the matrix).

11. Transdermal drug delivery system according to claim 1, wherein the matrix comprises 0.1 to 5.0, preferably 0.3 to 3 and especially 0.5 to 2.0% by weight of the crosslinking agent (based on the matrix).

12. Transdermal drug delivery system according to claim 1, wherein the system has a surface of 5 to 80, preferably 10 to 60 and especially 20 to 50 cm^2.

~~Summary~~ **ABSTRACT OF THE DISCLOSURE**

~~The concerns a~~A transdermal drug delivery system (TDS) comprising

- a cover which is impermeable for the active ingredient,
- a matrix containing oxybutynin as active ingredient and
- a facultative release liner.__; ~~wherein the~~The matrix further comprises
- an ~~Aloe Vera~~*Aloe vera* extract,
- a facultative skin care agent,
- a pressure sensitive adhesive and
- a cross linking agent for the adhesive.